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Pioglitazone for prevention of cardiovascular events in patients with stroke and pre-diabetes: implications for real-world practice

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Pioglitazone Therapy in Patients With Stroke and Prediabetes
A Post Hoc Analysis of the IRIS Randomized Clinical Trial

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Supplemental content

IMPORTANCE In the Insulin Resistance Intervention After Stroke (IRIS) randomized clinical trial, pioglitazone, an insulin-sensitizing agent, reduced the risk for recurrent stroke or myocardial infarction (MI) among patients with insulin resistance. However, insulin resistance is not commonly measured in clinical practice.

OBJECTIVE To analyze the effects of pioglitazone in patients with good adherence as well as intention-to-treat effects of pioglitazone in patients with prediabetes in the IRIS trial.

DESIGN, SETTING, AND PARTICIPANTS The IRIS trial was a randomized multicenter clinical trial in patients with prior stroke or transient ischemic attack as well as insulin resistance but not diabetes. Patients were enrolled from February 2005 to January 2013, and the median follow-up was 4.8 years. The post hoc analyses reported here were performed from June to September 2018. Per American Diabetes Association criteria, prediabetes was defined as having a hemoglobin A_{1c} level of 5.7% to 6.4% or fasting plasma glucose level of 100 mg/dL to 125 mg/dL (to convert to mmol/L, multiply by 0.0555). Good adherence was defined as taking 80% or more of the protocol dose. Fasting glucose and hemoglobin A_{1c}, used to define prediabetes, and adherence of 80% or higher, stipulated in the protocol as defining good adherence, were prespecified subgroups in the analysis plan.

INTERVENTIONS Participants were randomized to 15 mg of pioglitazone, with dose titrated to target of 45 mg daily, or matching placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was recurrent stroke or MI. Secondary outcomes included stroke, acute coronary syndrome, stroke/MI/hospitalization for heart failure, and progression to diabetes.

RESULTS Among 3876 participants analyzed in the IRIS trial, 2885 were included in this analysis (1456 in the pioglitazone cohort and 1429 in the placebo cohort). The mean (SD) age of patients was 64 (11) years, and 974 (66.9%) and 908 (63.5%) of patients were men in the pioglitazone and placebo cohort, respectively. In the prediabetic population with good adherence (644 of 1456 individuals [44.2%] in the pioglitazone group and 810 of 1429 [56.7%] in the placebo group), the hazard ratios (95% CI) were 0.57 (0.39-0.84) for stroke/MI, 0.64 (0.42-0.99) for stroke, 0.47 (0.26-0.85) for acute coronary syndrome, 0.61 (0.42-0.88) for stroke/MI/hospitalization for heart failure, and 0.18 (0.10-0.33) for progression to diabetes. There was a nonsignificant reduction in overall mortality, cancer, and hospitalization, a slight increase in serious bone fractures, and an increase in weight gain and edema. Intention-to-treat results also showed significant reduction of events but to a lesser degree. Hazard ratios (95% CI) were 0.70 (0.56-0.88) for stroke/MI, 0.72 (0.56-0.92) for stroke, 0.72 (0.52-1.00) for acute coronary syndrome, 0.78 (0.63-0.96), for stroke/MI/hospitalization for heart failure, and 0.46 (0.35 to 0.61) for progression to diabetes.

CONCLUSIONS AND RELEVANCE Pioglitazone may be effective for secondary prevention in patients with stroke/transient ischemic attack and with prediabetes, particularly in those with good adherence.

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Diabetes is an important risk factor for stroke.[1,2] Adverse cardiovascular effects of diabetes are associated with insulin resistance, which is present in 50% of patients with stroke or transient ischemic attack who do not have diabetes.[3] Insulin resistance is associated with increased blood pressure, serum low-density lipoprotein cholesterol, triglycerides, coagulation, inflammatory markers, platelet reactivity, reduced high-density lipoprotein cholesterol, and vascular reactivity.[4-6]

Pioglitazone also has antiatherosclerotic effects[7,8]; it reduces insulin resistance by activating peroxisome proliferator-activated receptors-γ and also causes partial minor activation of peroxisome proliferator-activated receptors-α,[9] which promotes uptake, use, and catabolism of fatty acids.[10]

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, fatal/nonfatal stroke was reduced by 47%.[11] In the Insulin Resistance Intervention After Stroke (IRIS) trial, pioglitazone reduced new-onset diabetes by half and reduced stroke or myocardial infarction (MI) by 24%.[12]

In a meta-analysis of studies in patients with stroke and insulin resistance, prediabetes, and diabetes mellitus, pioglitazone was associated with a 42% lower risk of recurrent stroke.[13] Adverse events that were more common in individuals using pioglitazone in the IRIS trial included weight gain, edema, and bone fractures.

Inclusion in the IRIS trial was based on the homeostatic model assessment of insulin resistance (HOMA-IR) score, a measure of insulin resistance (fasting blood glucose in milligrams per deciliter × fasting insulin level in milliunits per liter/405). Homeostatic model assessment of insulin resistance is not commonly measured, so the IRIS results may be perceived as having limited application in clinical practice.

Therefore, to translate the IRIS trial results to real-world practice, we present analyses for patients with prediabetes, as defined by the American Diabetes Association. Results for participants with prediabetes by the more conservative definitions of the World Health Organization (WHO) are presented in eTable 3, eTable 4, and the eFigure in Supplement 1. Because we wished to assess the potential benefit of pioglitazone in real-world practice, we emphasized the results in participants who were adherent to therapy, with adherence defined as taking 80% or more of the protocol dose over the duration of the study.

Key Points

Question Does pioglitazone reduce cardiovascular events in patients with prediabetes?

Findings In this post hoc analysis of 2885 individuals with prediabetes enrolled in a randomized clinical trial, there was a significant reduction of cardiovascular events and new-onset diabetes. The association was amplified in participants with good adherence (≥80% of protocol dose taken), with stroke/myocardial infarction reduced by 40%, stroke by 33%, and new-onset diabetes by 80%.

Meaning Pioglitazone may be an effective therapy for secondary stroke prevention in patients with prediabetes.

Methods

Study Design

In the IRIS trial,[12] insulin resistance was defined as a HOMA-IR score higher than 3. Participants without diabetes with ischemic stroke or transient ischemic attack who had insulin resistance were randomized 1:1 to placebo or pioglitazone. The dose of study drug was titrated up from 15 mg of pioglitazone per day or matching placebo to 45 mg per day over 3 months, and participants continued receiving the highest dose tolerated. The present study is a post hoc, exploratory subgroup analysis. Fasting glucose and hemoglobin A_{1c} (HbA_{1c}), used to define prediabetes, and adherence of 80% or higher, stipulated in the protocol as defining good adherence, were prespecified subgroups in the analysis plan. The statistical analysis plan is available in Supplement 2.

Trial Conduct and Ethics

The study was approved by the local ethics committee at each site. Participants gave written consent. The trial was monitored by an independent data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke, which funded the study.

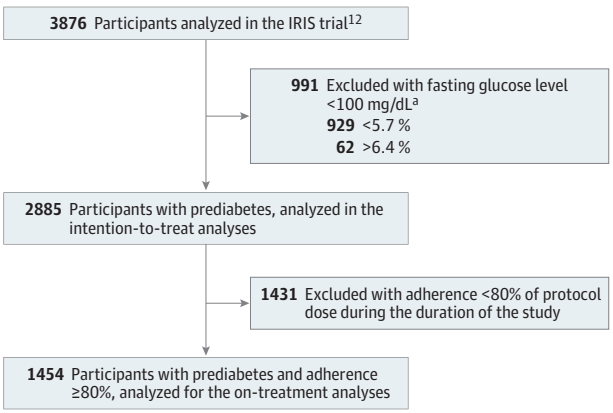
Patient Population

Of 3876 participants in the IRIS trial, we analyzed results of pioglitazone therapy in patients with prediabetes based on the American Diabetes Association criteria.[14] Selection of participants is shown in **Figure 1**. Results based on the WHO definition[15,16] are presented in eTable 3, eTable 4, and the eFigure in Supplement 1.

Definitions

By the American Diabetes Association definition, patients are considered to have prediabetes if the glycosylated HbA_{1c} level is 5.7% to 6.4% or the fasting plasma glucose level is 100 mg/dL

Figure 1. CONSORT Diagram



IRIS indicates Insulin Resistance Intervention After Stroke.

[a] Prediabetes was defined by American Diabetes Association criteria: hemoglobin A_{1c} 5.7% to 6.4% or fasting plasma glucose level 100 mg/dL to 125 mg/dL (to convert to millimoles per liter, multiply by 0.0555).

Table 1. Baseline Characteristics of Participants With Adherence of 80% or More

Risk Factor	Pioglitazone Group (n = 644)	Placebo Group (n = 810)	*P* Value
Continuous variables, mean (SD)[a]			
Age, y	63.23 (9.73)	64.04 (10.15)	.13
Fasting glucose level, mg/dL	101.10 (9.95)	100.78 (9.59)	.54
Hemoglobin A_{1c} level, %	5.92 (0.33)	5.91 (0.33)	.61
HOMA-IR score	5.66 (2.86)	5.49 (2.48)	.22
Systolic pressure, mm Hg	133.94 (17.56)	132.58 (16.42)	.13
Diastolic pressure, mm Hg	80.24 (10.89)	78.57 (10.03)	.002
Total cholesterol level, mg/dL	158.75 (37.72)	157.93 (35.87)	.67
Triglycerides level, mg/dL	140.42 (67.87)	138.18 (68.17)	.53
HDL-C level, mg/dL	45.31 (11.19)	46.67 (11.93)	.03
LDL-C level, mg/dL	85.52 (31.61)	83.76 (30.47)	.28
BMI	30.05 (5.58)	30.22 (5.31)	.47
Categorical variables, No. (%)[b]			
Men	491 (76.2)	572 (70.6)	.02
Smoker at baseline	102 (15.9)	95 (11.7)	.02

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.0113; cholesterol to millimoles per liter, by 0.0259.

[a] Using analysis of variance.

[b] Using χ^2.

to 125 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or the 2-hour glucose tolerance test result is more than 140 mg/dL to 199 mg/dL.[16] In the IRIS trial, patients were classified as having prediabetes for the current study based solely on HbA_{1c} and fasting glucose measures.[14] Prediabetes was defined by the WHO criteria as an HbA_{1c} level of 6% to 6.4% or fasting glucose level of 110 mg/dL to 125 mg/dL.[15]

Good adherence was specified in the IRIS protocol as taking 80% or more of the protocol dose over the duration of the study as measured by pill counts on returned bottles. This is one of several common definitions of good adherence across trials.[17]

The primary end point was recurrent fatal or nonfatal stroke, or MI. Secondary outcomes were recurrent stroke; acute coronary syndrome; the composite of stroke/MI/hospitalization for heart failure; and the progression to diabetes. In these analyses, we used updated criteria for stroke and MI.[18,19] Preselected safety events (ie, bone fracture, heart failure, and cancer) were adjudicated by the members of independent committees in a blinded fashion.

Statistical Methods

Categorical variables were summarized as percentage, and differences between groups were compared by the χ^2 test. Continuous variables were summarized as mean (SD); differences between groups were analyzed by analysis of variance. Hazard analyses were completed by Cox regression. Relative risk reductions (RRRs) were calculated as percent reduction of events. Cumulative event-free rates were calculated by the Kaplan-Meier method.[20] A 2-sided *P* value less than .05 was regarded as significant. Statistical tests were performed using SPSS, version 25 (IBM Corporation) and SAS software, version 9.4 (SAS Institute Inc). As it is known that patients with good adherence tend to have better outcomes,[21] we compared participants with good adherence in both arms of the study.

Results

By the American Diabetes Association criteria, there were 2885 participants with prediabetes and 1410 with prediabetes by the more restrictive WHO criteria. Results presented here are for patients with prediabetes by the US criteria; Figure 1 shows the selection of the subgroups. Results for participants with prediabetes by the WHO criteria were very similar, although less statistically significant, and are presented in eTable 3, eTable 4, and the eFigure in Supplement 1.

Participants with prediabetes had higher levels of glycosylated HbA_{1c} than those without prediabetes (mean [SD], 5.92% [0.34%] vs 5.47% [0.35%]) and higher HOMA-IR scores (mean [SD], 5.68 [2.87] vs 4.78 [2.19]), the latter indicating greater insulin resistance. Baseline characteristics of the participants with good adherence are shown in **Table 1**; characteristics of the participants in the intention-to-treat (ITT) analysis are shown in eTable 5 in Supplement 1.

Analyses for the Subgroup With Adherence of 80% or More

Among 1454 participants with prediabetes and good adherence to the protocol dose, 644 (44.3%) were in the pioglitazone group and 810 (55.7%) in the placebo group. The mean (SD) age of patients was 63 (10) years in the pioglitazone group and 64 (10) years in the placebo group. Patients with good adherence taking pioglitazone were more likely to be men (491 [76.2%] vs 572 [70.6%]), were more likely to be smokers (102 [15.9%] vs 95 [11.7%]), and had higher diastolic pressures and lower baseline high-density lipoprotein cholesterol (Table 1). Fasting blood glucose level, systolic and diastolic blood pressure, triglyceride level, and high-density lipoprotein cholesterol level were all significantly better during treatment with pioglitazone (eTable 2 in Supplement 1). Reductions in outcomes and RRRs with pioglitazone were for stroke/MI, from 83 (10.2%) to 39 (6.1%), RRR = 40%; for stroke, 61 (7.5%) to 32

Table 2. Hazard Ratios in Cox Regression for On-Treatment and Intention-to-Treat Analyses

Variable	Hazard Ratio (95% CI)	*P* Value	NNT
Adherence ≥80%			
Stroke/MI	0.57 (0.39-0.84)	.004	24
Stroke	0.64 (0.42-0.99)	.04	39
Acute coronary syndrome	0.47 (0.26-0.85)	.01	40
Stroke/MI/HF hospitalization	0.61 (0.42-0.88)	.008	26
New-onset diabetes	0.18 (0.10-0.33)	<.001	12
Intention to treat			
Stroke/MI	0.70 (0.56-0.88)	.002	28
Stroke	0.72 (0.56-0.93)	.01	39
Acute coronary syndrome	0.72 (0.52-1.00)	.052	62
Stroke/MI/HF hospitalization	0.78 (0.63-0.96)	.02	34
New-onset diabetes	0.46 (0.35-0.61)	<.001	19

Abbreviations: HF, heart failure; MI, myocardial infarction; NNT, number needed to treat.

(5%), RRR = 33%; for acute coronary syndrome, 39 (4.8%) to 15 (2.3%), RRR = 52%; and for stroke/MI/hospitalization for heart failure, 84 (10.4%) to 42 (6.5%), RRR = 38%. New-onset diabetes was reduced by pioglitazone from 82 (10.1%) to 13 (2.0%), RRR = 80%. Hazard ratios with 95% CI and numbers needed to treat (NNT) for statistically significant differences are shown in **Table 2** and time-to-event curves in **Figure 2**.

Effects of pioglitazone were numerically greater among IRIS participants with prediabetes than in those without prediabetes; however, the differences were not significant (eTable 1 in Supplement 1). The results for patients with prediabetes by the WHO definition were similar to the results for prediabetes defined by US criteria but with the smaller sample size were not statistically significant except for new-onset diabetes (eTable 2, eTable 3, and eFigure in Supplement 1).

Intention-to-Treat Analyses

Among 2885 participants with prediabetes, 1456 (50.5%) were randomized to pioglitazone and 1429 (49.5%) to placebo. Baseline characteristics of the patients with prediabetes by randomized treatment group are shown in eTable 5 in Supplement 1. The mean (SD) age of patients was 64 (11) years, and 974 (66.9%) and 908 (63.5%) were men in the pioglitazone group and placebo group, respectively. Reductions in outcomes and RRRs with pioglitazone were for stroke/MI, from 179 (12.5%) to 130 (8.9%), RRR = 29%; for stroke, 135 (9.4%) to 100 (6.9%), RRR = 27%; for acute coronary syndrome, 84 (5.9%) to 62 (4.3%), RRR = 27%; and for stroke/MI/hospitalization for heart failure, 193 (13.5%) to 154 (10.6%), RRR = 22%. New-onset diabetes was reduced by pioglitazone from 142 (9.9%) to 69 (4.7%), RRR = 53%. Hazard ratios and 95% CI as well as NNT for statistically significant results are shown in Table 2. For patients without prediabetes, effects of pioglitazone were attenuated but not statistically different compared with patients with prediabetes (eTable 1 in Supplement 1).

Adverse Outcomes

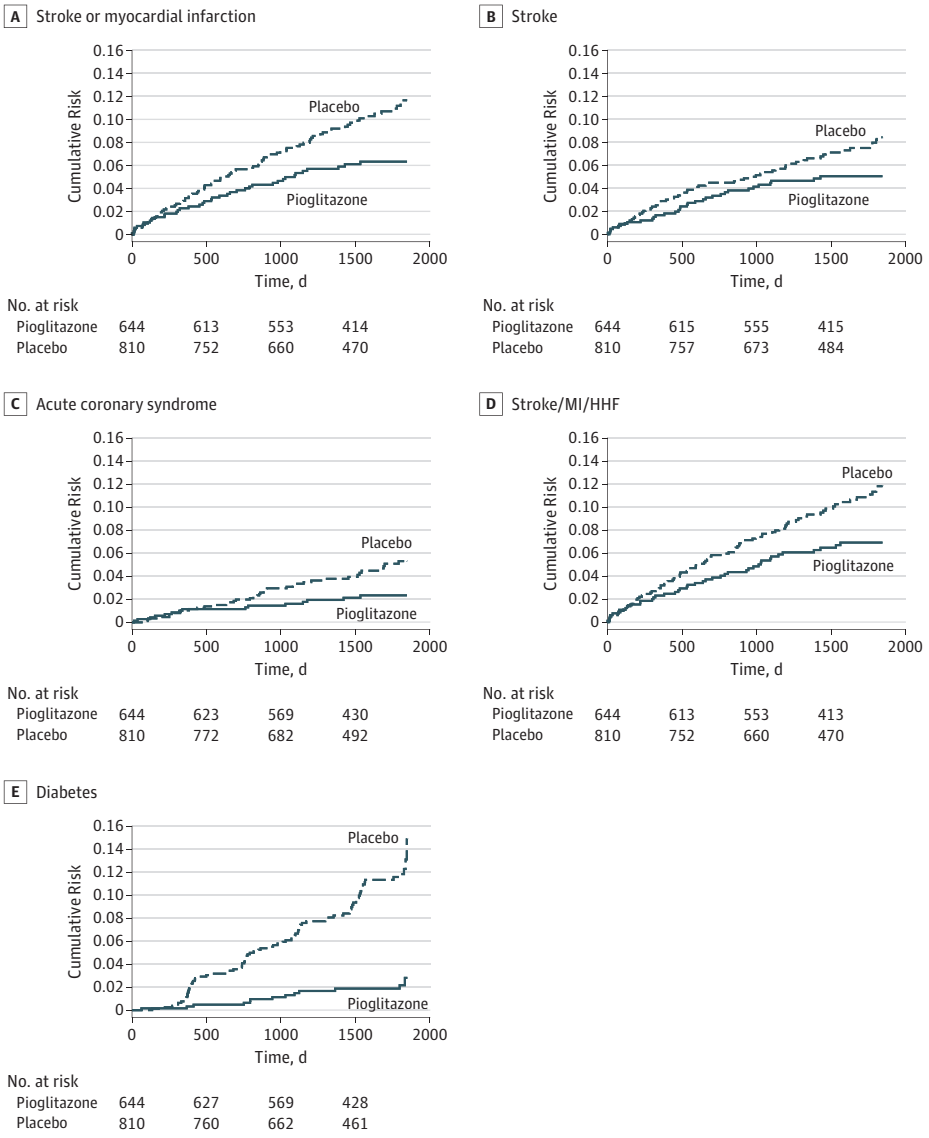
Among the participants with good adherence, serious bone fractures occurred in 23 patients (3.6%) in the pioglitazone group vs 23 patients (2.8%) in the placebo group. Weight gain of 10% or more occurred in 192 (29.8%) in the pioglitazone group vs 97 (12.0%) in the placebo group; edema occurred in 188 (29.2%) in the pioglitazone group vs 175 (21.6%) in the placebo group. There was a slight and nonsignificant reduction in all-cause mortality, cancer, and hospitalization with pioglitazone, and no significant increase in heart failure. **Table 3** shows hazard ratio and 95% CI, and number needed to harm, for statistically significant differences. Adverse events for the ITT analysis followed the same pattern (eTable 5 in Supplement 1).

Discussion

Among IRIS study participants with prediabetes and good adherence, pioglitazone reduced stroke/MI by 40%, stroke by 33%, acute coronary syndrome by 52%, and new-onset diabetes by 80% over a median follow-up of 4.8 years. The effect sizes in the ITT analysis of those with prediabetes were smaller (29%, 27%, 27%, and 53%, respectively). These findings were observed despite a higher proportion of men and smokers, higher diastolic blood pressures, and lower high-density lipoprotein cholesterol levels among individuals with good adherence assigned to receive pioglitazone. These associations of pioglitazone in the cohort with good adherence were greater than the associations observed in the ITT cohort or in the full trial cohort probably because this was an analysis of participants with good adherence and also perhaps because participants with prediabetes had higher HbA_{1c} level and HOMA-IR scores than those without prediabetes. As shown in Figure 2, the benefit of pioglitazone continued to increase over time, suggesting that even greater benefits might have been shown with longer follow-up. Some or much of this may have been due to prevention of diabetes over time. A 2018 study from the Swedish National Diabetes Register reported that in individuals with diabetes, the strongest predictor of cardiovascular adverse events was HbA_{1c}.[22]

A question that arises from our findings is whether patients can be selected for pioglitazone therapy after stroke or transient ischemic attack based on prediabetes rather than the HOMA-IR test. It is not possible to provide a definitive answer to this question because all of the patients in our secondary analysis were enrolled in the study based on a HOMA-IR criterion. However, we believe such a strategy is reasonable

Figure 2. Time to First Event for Participants With 80% or More Adherence



A, Stroke or myocardial infarction (hazard ratio [HR] 0.57; 95% CI, 0.39-0.84; *P* = .004). B, Stroke (HR, 0.64; 95% CI, 0.42-0.99; *P* = .04). C, Acute coronary syndrome (HR, 0.47; 95% CI, 0.26-0.85; *P* = .01). D, Stroke/myocardial infarction (MI)/hospitalization for heart failure (HHR) (HR, 0.61; 95% CI, 0.42-0.88; *P* = .008). E, New-onset diabetes (HR, 0.18; 95% CI, 0.10-0.33; *P* < .001).

for 3 reasons: (1) HbA_{1c} level correlates well with measures of insulin resistance, (2) most patients with recent ischemic stroke and prediabetes have insulin resistance,[3] and (3) in the IRIS Trial, HOMA-IR score was inversely and paradoxically correlated with magnitude of treatment effect.[23] If a criterion based on HbA_{1c} results in administration of pioglitazone to patients with lesser severity of insulin resistance, our data suggest this may not diminish the benefit of pioglitazone. Of course, the only way to provide a definitive answer would be to conduct a new trial with entry criteria based on HbA_{1c} level rather than HOMA-IR score. An interim strategy might be to use pioglitazone for patients with a high threshold for HbA_{1c} (eg, 6.0%) to select patients with a very high probability of advanced insulin resistance.

Participants with prediabetes had greater benefit from pioglitazone than those in the IRIS trial, although adherence was slightly less. In the IRIS trial, the percentage of participants with good adherence was 45.2% in the pioglitazone cohort vs 58.2% in the placebo cohort. In participants with prediabetes, 44.5% in the pioglitazone group had good adherence vs 57.3% in the placebo group. Notably, this is the first time, to our knowledge, that any glucose-lowering treatment has been demonstrated to reduce vascular events in a population with prediabetes. Prediabetes is a recognized risk factor for ischemic stroke,[24] especially for recurrent stroke. A 2018 study also found that subclinical cerebral infarcts were more than 60% more common in individuals with prediabetes than in those with euglycemia and that this relative increase was nearly as high as observed in those with overt diabetes.[25] Accordingly, our data support the notion of early treatment of prediabetes to improve clinical outcomes in those with established vascular disease.

Although ITT analysis is usually regarded as de rigeur, there are good reasons to also perform analyses that show the po-

Table 3. Adverse Events by Severity for Participants With Prediabetes by US/American Diabetes Association Criteria, by Treatment Group

Event	No. (%) Pioglitazone Group	Placebo Group	*P* Value	NNH[a]
Adherence >80%	n = 644	n = 810	NA	NA
Serious adverse events				
All-cause mortality	42 (6.5)	57 (7.0)	.70	NA
Hospitalization	262 (40.7)	353 (43.6)	.27	NA
Incident cancer	33 (5.1)	53 (6.5)	.25	NA
Bone fracture[b]	23 (3.6)	23 (2.8)	.43	NA
Heart failure[c]	4 (0.6)	2 (0.2)	.27	NA
Other adverse events[d]				
Other bone fracture	43 (6.7)	37 (4.6)	.08	NA
Other heart failure	1 (0.2)	3 (0.4)	.44	NA
Weight gain[e]	192 (29.8)	97 (12.0)	<.001	6
Edema[f]	188 (29.2)	175 (21.6)	<.001	13
Intention to treat	n = 1456	n = 1429	NA	NA
Serious adverse events				
All-cause mortality	108 (7.4)	111 (7.8)	.72	NA
Hospitalization	674 (46.3)	703 (49.2)	.12	NA
Incident cancer	99 (6.8)	110 (7.7)	.35	NA
Bone fracture[b]	71 (4.9)	46 (3.2)	.02	59
Heart failure[c]	39 (2.7)	31 (2.2)	.37	NA
Other adverse events[d]				
Other bone fracture	96 (6.6)	74 (5.2)	.11	NA
Other heart failure	21 (1.4)	24 (1.7)	.61	NA
Weight gain[e]	382 (26.2)	182 (12.7)	<.001	7
Edema[f]	541 (37.2)	360 (25.2)	<.001	8

Abbreviations: NA, not applicable; NNH, number needed to harm.

[a] Computed only for statistically significant differences.

[b] Adjudicated bone fracture resulting in hospitalization, surgery, or procedure.

[c] Adjudicated episode of heart failure causing hospitalization or death.

[d] Adjudicated events that do not meet criteria for serious as defined above.

[e] Weight change of 10% of more from baseline at any time in trial.

[f] Self-reported new or worse swelling of feet or lower legs.

tential of a treatment among persons able to take it. Hernán and Robins[26] discussed this issue, saying that ITT analysis may not be directly relevant for guiding decisions in clinical settings with different adherence patterns. Sheiner and Rubin[27] made the distinction between "use effectiveness" (the result of prescribing a medication) and "method effectiveness" (the result of taking a medication). They pointed out that for the purpose of treating individual patients, method effectiveness was a more useful pharmacologic characteristic. This may be particularly true for drugs, which, like pioglitazone, have adverse effects that limit adherence in some patients but not in others. For patients who can take pioglitazone, it appears to be very beneficial; some patients may not be able to take it if fluid retention is excessive.

As seen in Table 3, a common adverse effect of pioglitazone is edema, which accounts for much (but not all) of the weight gain. Although we did not observe an increase in heart failure with pioglitazone in the IRIS trial, there have been concerns about heart failure as an adverse effect of pioglitazone. There appear to be 2 mechanisms contributing to edema: salt and water retention due to effects on the renal tubular epithelial sodium channel and other effects in the collecting duct[28] and perhaps increased vascular permeability.[29]

There are maneuvers that can be implemented to minimize the problem of fluid retention. The simplest would be to use a lower dose of pioglitazone. The usual doses of pioglitazone are 15 mg, 30 mg, or 45 mg daily, but a 2017 review indicated that 7.5 mg daily confers much of the benefit of pioglitazone with less weight gain and fluid retention.[30] Initiating the drug with dose titration, with a prescription that specifies repeats of the dose that did not cause a problem is 1 approach to mitigating the problem with fluid retention. Another is the use of amiloride, a specific antagonist of epithelial sodium channel. The centrality of the renal tubular epithelial sodium channel to salt and water retention and the importance of considering the use of amiloride, a seldom-used drug, were recently reviewed.[31] It seems likely that amiloride, a specific antagonist of epithelial sodium channel,[32] may be useful in counteracting the weight gain and fluid retention due to pioglitazone.[33] (Vigilance should be exercised with regard to hyperkalemia in patients with impaired renal function.) Amiloride was reported to be more efficacious than spironolactone in reducing fluid retention with pioglitazone.[33]

From the perspective of the payer, with regard to direct cost of medication, what matters more is what happens when patients use a treatment since there are no medication costs for those who do not. Third-party payers who also cover the costs of costly complications such as stroke should also consider the cost of not taking medications. The economic benefits of pioglitazone with regard to prevention of MI/stroke (NNT, 24), stroke (NNT, 39), and diabetes (NNT, 12) may be offset somewhat by the cost of events such as fractures (number needed to harm, 125). Myocardial infarction and stroke are very costly,

so the balance of NNTs for beneficial outcomes and numbers needed to harm for adverse outcomes would suggest cost utility for pioglitazone, but we have not yet conducted a cost-utility calculation. To achieve the greatest benefit of pioglitazone in prediabetes it would probably be better to use the US definition rather than the WHO definition.

Limitations

There are limitations to our analyses. All the participants in the IRIS trial had insulin resistance; these analyses pertain to the subgroup with prediabetes, who had significantly higher HOMA-IR scores. We cannot know the effectiveness of pioglitazone in patients with prediabetes and HOMA-IR scores less than or equal to 3, although this would be an infrequent scenario. Also, the diabetes end point was simply based on fasting glucose levels and patient reports. Hemoglobin A_{1c} testing was not performed after the baseline visit, and oral glucose tolerance testing was not part of the protocol. As such, our diagnostic rate for new-onset diabetes was likely reduced, although this should not have introduced a bias.

Conclusions

Pioglitazone appears to reduce the risk of recurrent stroke or MI, recurrent stroke, acute coronary syndrome, and diabetes in patients with insulin resistance and prior stroke/transient ischemic attack and prediabetes, particularly in individuals who adhere to therapy. These benefits appear to outweigh the risks of fracture and fluid retention.

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REFERENCES

1. Burchfiel CM, Curb JD, Rodriguez BL, Abbott RD, Chiu D, Yano K. Glucose intolerance and 22-year stroke incidence. The Honolulu Heart Program. *Stroke*. 1994;25(5):951-957. doi:10.1161/01.STR.25.5.951

2. Janghorbani M, Hu FB, Willett WC, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study. *Diabetes Care*. 2007;30(7):1730-1735. doi:10.2337/dc06-2363

3. Kernan WN, Inzucchi SE, Viscoli CM, et al. Impaired insulin sensitivity among nondiabetic patients with a recent TIA or ischemic stroke. *Neurology*. 2003;60(9):1447-1451. doi:10.1212/01.WNL.0000063318.66140.A3

4. Mather KJ, Steinberg HO, Baron AD. Insulin resistance in the vasculature. *J Clin Invest*. 2013;123(3):1003-1004. doi:10.1172/JCI67166

5. Semenkovich CF. Insulin resistance and atherosclerosis. *J Clin Invest*. 2006;116(7):1813-1822. doi:10.1172/JCI29024

6. Kernan WN, Inzucchi SE, Viscoli CM, Brass LM, Bravata DM, Horwitz RI. Insulin resistance and risk for stroke. *Neurology*. 2002;59(6):809-815. doi:10.1212/WNL.59.6.809

7. Spencer M, Yang L, Adu A, et al. Pioglitazone treatment reduces adipose tissue inflammation through reduction of mast cell and macrophage number and by improving vascularity. *PLoS One*. 2014;9(7):e102190. doi:10.1371/journal.pone.0102190

8. Zhang MD, Zhao XC, Zhang YH, et al. Plaque thrombosis is reduced by attenuating plaque inflammation with pioglitazone and is evaluated by fluorodeoxyglucose positron emission tomography. *Cardiovasc Ther*. 2015;33(3):118-126. doi:10.1111/1755-5922.12119

9. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351(11):1106-1118. doi:10.1056/NEJMra041001

10. Berger J, Moller DE. The mechanisms of action of PPARs. *Annu Rev Med*. 2002;53:409-435. doi:10.1146/annurev.med.53.082901.104018

11. Wilcox R, Bousser MG, Betteridge DJ, et al; PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke*. 2007;38(3):865-873. doi:10.1161/01.STR.0000257974.06317.49

12. Kernan WN, Viscoli CM, Furie KL, et al; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;374(14):1321-1331. doi:10.1056/NEJMoa1506930

13. Lee M, Saver JL, Liao HW, Lin CH, Ovbiagele B. Pioglitazone for secondary stroke prevention: a systematic review and meta-analysis. *Stroke*. 2017;48(2):388-393. doi:10.1161/STROKEAHA.116.013977

14. American Diabetes Association. 2: Classification and diagnosis of diabetes. *Diabetes Care*. 2016;39 (suppl 1):S13-S22. doi:10.2337/dc16-S005

15. Punthakee Z, Goldenberg R, Katz P; Diabetes Canada Clinical Practice Guidelines Expert Committee. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Can J Diabetes*. 2018;42(suppl 1):S10-S15. doi:10.1016/j.jcjd.2017.10.003

16. Morris DH, Khunti K, Achana F, et al. Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. *Diabetologia*. 2013;56(7):1489-1493. doi:10.1007/s00125-013-2902-4

17. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*. 2006; 333(7557):15. doi:10.1136/bmj.38875.675486.55

18. Young LH, Viscoli CM, Curtis JP, et al; IRIS Investigators. Cardiac outcomes after ischemic stroke or transient ischemic attack: effects of pioglitazone in patients with insulin resistance without diabetes mellitus. *Circulation*. 2017;135 (20):1882-1893. doi:10.1161/CIRCULATIONAHA.116.024863

19. Yaghi S, Furie KL, Viscoli CM, et al; IRIS Trial Investigators. Pioglitazone prevents stroke in patients with a recent transient ischemic attack or ischemic stroke: a planned secondary analysis of the IRIS trial (Insulin Resistance Intervention After Stroke). *Circulation*. 2018;137(5):455-463. doi:10.1161/CIRCULATIONAHA.117.030458

20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481. doi:10.1080/01621459.1958.10501452

21. Armstrong EJ, Chen DC, Westin GG, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc*. 2014;3(2):e000697. doi:10.1161/JAHA.113.000697

22. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018; 379(7):633-644. doi:10.1056/NEJMoa1800256

23. Inzucchi SE, Viscoli CM, Young LH, et al. What mediated pioglitazone's cardiovascular benefit in the iris trial? Paper presented at: American Diabetes Association 78th Scientific Sessions 2018; June 25, 2018; Orlando, FL.

24. Fonville S, Zandbergen AA, Koudstaal PJ, den Hertog HM. Prediabetes in patients with stroke or transient ischemic attack: prevalence, risk and clinical management. *Cerebrovasc Dis*. 2014;37(6): 393-400. doi:10.1159/000360810

25. van Agtmaal MJM, Houben AJHM, de Wit V, et al. Prediabetes is associated with structural brain abnormalities: the Maastricht Study. *Diabetes Care*. 2018;41(12):2535-2543. doi:10.2337/dc18-1132

26. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med*. 2017;377(14): 1391-1398. doi:10.1056/NEJMsm1605385

27. Sheiner LB, Rubin DB. Intention-to-treat analysis and the goals of clinical trials. *Clin Pharmacol Ther*. 1995;57(1):6-15. doi:10.1016/0009-9236(95)90260-0

28. Bełtowski J, Rachańczyk J, Włodarczyk M. Thiazolidinedione-induced fluid retention: recent insights into the molecular mechanisms. *PPAR Res*. 2013;2013:628628. doi:10.1155/2013/628628

29. Nakamura A, Osonoi T, Terauchi Y. Relationship between urinary sodium excretion and pioglitazone-induced edema. *J Diabetes Investig*. 2010;1(5):208-211. doi:10.1111/j.2040-1124.2010.00046.x

30. Adachi H, Katsuyama H, Yanai H. The low dose (7.5mg/day) pioglitazone is beneficial to the improvement in metabolic parameters without weight gain and an increase of risk for heart failure. *Int J Cardiol*. 2017;227:247-248. doi:10.1016/j.ijcard.2016.11.126

31. Akintunde A, Nondi J, Gogo K, et al. Physiological phenotyping for personalized therapy of uncontrolled hypertension in Africa. *Am J Hypertens*. 2017;30(9):923-930. doi:10.1093/ajh/hpx066

32. Spence JD, Rayner BL. Hypertension in blacks: individualized therapy based on renin/aldosterone phenotyping. *Hypertension*. 2018;72(2):263-269. doi:10.1161/HYPERTENSIONAHA.118.11064

33. Viswanathan V, Mohan V, Subramani P, et al. Effect of spironolactone and amiloride on thiazolidinedione-induced fluid retention in South Indian patients with type 2 diabetes. *Clin J Am Soc Nephrol*. 2013;8(2):225-232. doi:10.2215/CJN.06330612